*IN THE UNITED STATES PATENT AND TRADEMARK OFFICE*

| | |
|---|---|
| Applicant: | Ray W. Wood et al. |
| Title: | METHODS OF ADMINISTERING LIQUID DROPLET AEROSOLS OF NANOPARTICULATE DRUGS |
| Appl. No.: | 09/577,489 |
| Filing Date: | 5/25/2000 |
| Examiner: | James Henry Alstrum Acevedo |
| Art Unit: | 1616 |
| Confirmation Number: | 7761 |

DECLARATION UNDER 37 C.F.R. §1.132

The undersigned, H. William Bosch, hereby declares as follows:

**I. Background of H. William Bosch**

1. I received my Ph.D. degree in 1987 from the University of Pennsylvania in chemistry. I have been working in the field of nanoparticulate drug technology since 1991, when I joined Sterling Winthrop Pharmaceuticals Research Division.

2. The portion of Sterling Winthrop Pharmaceuticals Research Division involved in nanoparticulate drug technology was sold and became known as NanoSystems. This business was then sold and became known as Elan Drug Technologies. Intellectual property developed at Elan Drug Technologies is owned by Elan Pharma International Ltd., which is the assignee of the above-referenced patent application.

3. Currently I am the Director of Pharmaceutical Research at iCeutica, with offices at 1 Crescent Drive, Suite 400, Navy Yard Corporate Center, Philadelphia PA 19112.

## II. Nebulization of Beclomthasone Formulations

5. Three beclomethasone diproprionate (BDP) formulations comprising polyvinyl alcohol as a surface modifier were tested for nebulization. A compressed-air or "jet" nebulizer (Puritan-Bennett Raindrop nebulizer) was used. The nebulizers contained a volume of about 2 ml of the formulation to be tested. The formulations are detailed in Table 1. Formulation Micro I contained unmilled, raw beclomethasone diproprionate particles (obtained from Sigma Chemical Company), which have a mean particle size of about 10.5 μm. Formulations Nano II and Nano III contained nanoparticulate beclomethasone diproprionate particles having an effective average particle size in the range of between 230 nm and 280 nm, with a standard deviation of between 40 nm and 110 nm. Polyvinyl Alcohol (PVA) was used as a surface modifier for the nanoparticulate beclomethasone diproprionate formulations Nano II and Nano III.

**Table 1**

| Formulation | Form | Polyvinyl Alcohol Concentration (w/w) | Test Volume (ml) |
|---|---|---|---|
| **Micro I** | Suspension comprising raw, micronized beclomethasone diproprionate particles | 2.5% | 1.85 |
| **Nano II** | Aqueous dispersion containing nanoparticulate beclomethasone diproprionate particles and polyvinyl alcohol | 2.5% | 1.85 |
| **Nano III** | Aqueous dispersion containing nanoparticulate beclomethasone diproprionate particles and polyvinyl alcohol | 0.1% | 1.85 |

6. The nebulization output for each formulation is detailed in Table 2.

**Table 2**

| Formulation | BDP Fraction Remaining in the nebulization device | BDP Fraction on Impactor (corresponding to amount of drug delivered) |
|---|---|---|
| **Micro I** | ~89% | ~8% |
| **Nano II** | ~77% | ~18% |
| **Nano III** | ~62% | ~17% |

7. The data in column 2 of Table 2 demonstrate that a significantly higher fraction of microparticulate BDP composition than nanoparticulate BDP composition remained in the nebulizer when comparing experiments with equivalent test volumes. Specifically, for nanoparticulate BDP compositions Nano II and Nano III, about 77% and about 62% BDP remained in the nebulizer respectively. In contrast, about 89% of BDP remained in the nebulizer for the microparticulate BDP composition Micro I. Thus, the nanoparticulate BDP compositions exhibited 13% to 30% ***decreases*** in drug remaining in the nebulizer as compared to the microparticulate BDP formulation.

8. The data in column 3 of Table 2 demonstrate that when comparing experiments with equivalent test volumes, a greater fraction of each of the nanoparticulate BDP formulations reached the impactor as compared to the microparticulate BDP formulation. Specifically, only about 8% of the microparticulate BDP formulation (Micro I) reached the impactor (which corresponds to the amount of drug delivered to a patient upon aerosol administration). In striking contrast, about 17% to about 18% respectively of the nanoparticulate BDP formulations Nano III and Nano II reached the impactor, demonstrating 113% to 125% ***increases*** in drug delivery as compared to the microparticulate BDP formulation.

## III. Delivery of Beclomethasone Formulations

9. The respirable fraction of an exemplary nanoparticulate beclomethasone dipropionate composition of the claimed invention delivered via an ultrasonic nebulizer was compared with that of a commercially available formulation containing microparticulate beclomethasone dipropionate (Vanceril®) delivered via a propellant-based metered-dose-inhaler (MDI).

10. Conventionally, an ultrasonic nebulizer was used for delivery of solution aerosols but was not feasible for delivering water-insoluble active agents due to a lack of efficient aerosolization.

11. The claimed nanoparticulate beclomethasone dipropionate composition was capable of being delivered by an ultrasonic nebulizer. Unexpectedly, superior delivery efficiency of the claimed nanoparticulate beclomethasone dipropionate composition was achieved in comparison to the commercial formulation, Vanceril®, delivered by a propellant-based MDI, as detailed below.

12. The exemplary nanoparticulate beclomethasone dipropionate composition comprised 1.25% w/w beclomethasone dipropionate and 0.25% w/w tyloxapol as the surface modifier. Vanceril® contained micronized beclomethasone dipropionate suspended in propellants. The particle size distributions of BDP in the formulations are detailed in Table 3.

**Table 3**

| Formulations | Mean (nm) | 90% < (nm) | 10% < (nm) |
|---|---|---|---|
| **Vanceril®** | 1960 | 4060 | 600 |
| **Nanoparticulate Beclomethasone Dipropionate Composition** | 164 | 228 | 103 |

13. The deposition of beclomethasone dipropionate per actuation is described in Table 4.

**Table 4**

| | Vanceril® µg/act. (range) | Nano BDP screen #1 µg/act. (range) | % of change relative to Vanceril® | Nano BDP screen #2 µg/act. (range) | % of change relative to Vanceril® |
|---|---|---|---|---|---|
| **Throat deposition** | 19.2 (0.50) | 2.85 (2.50) | - 85% | 11.4 (11.4) | - 41% |
| **Emitted dose** | 36.1 (2.50) | 31.7 (4.37) | - 12% | 67.4 (1.97) | + 87% |
| **Respirable dose** | 12.8 (1.70) | 22.6 (1.74) | + 77% | 39.4 (3.42) | + 208% |

14. As demonstrated in Table 4, the nanoparticulate beclomethasone dipropionate composition delivered by an ultrasonic nebulizer increased the respirable dose by 77% to 208% in comparison to the microparticulate, commercial formulation Vanceril®. At the same time, the nanoparticulate beclomethasone dipropionate composition delivered by an ultrasonic nebulizer decreased the throat deposition by 41% to 85% in comparison to the microparticulate, commercial formulation Vanceril®, resulting in a significantly higher delivery efficiency.

15. Although Table 4 shows that the emitted dose of the nanoparticulate beclomethasone dipropionate composition delivered by an ultrasonic nebulizer, screen #1, exhibited a slight decrease of 12% in comparison to the microparticulate, commercial formulation Vanceril®, the respirable dose was nevertheless increased by 77% and throat deposition was decreased by 85%. Accordingly, the slight decrease in emitted dose of the nanoparticulate beclomethasone dipropionate did not adversely affect the improved delivery efficiency.

16. The deposition of beclomethasone dipropionate as a percentage of emitted dose is further detailed in Table 5.

| Table 5 | | | | | |
|---|---|---|---|---|---|
| | Vanceril® (% dose) | Nano BDP screen #1 (% dose) | % of change relative to Vanceril® | Nano BDP screen #2 (% dose) | % of change relative to Vanceril® |
| **Throat deposition** | 53.2 (2.30) | 8.99 (6.67) | - 83% | 10.4 (8.19) | - 80% |
| **Respirable dose** | 34.8 (3.40) | 71.6 (15.3) | + 106% | 55.9 (6.60) | + 61% |

17. As demonstrated in Table 5, when the deposition of beclomethasone dipropionate was viewed as a percentage of emitted dose, the nanoparticulate beclomethasone dipropionate composition delivered by an ultrasonic nebulizer increased the respirable dose by 61% to 106% and decreased the throat deposition by 80% to 83% in comparison to the microparticulate, commercial formulation Vanceril®.

## CONCLUSION

18. The data described herein demonstrate that nanoparticulate beclomethasone diproprionate formulations unexpectedly achieved more efficient nebulization and delivery than the control formulations comprising microparticulate beclomethasone diproprionate.

19. I declare that the statements made herein of my knowledge are true and all statements on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therein.

H. William Bosch

H. William Bosch

31 March 2011

Date